CLAIMS

What is claimed is:

1. A method for treating diabetes mellitus, comprising:

administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity.

2. A method for treating diabetes mellitus, comprising:

administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity wherein said agent enhances insulin secretion.

3. A method for treating diabetes mellitus, comprising:

administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity wherein said agent enhances insulin secretion that is stimulated by glucose.

4. A method for treating diabetes mellitus, comprising:

administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity wherein said agent enhances insulin secretion that is stimulated by a supraphysiological glucose concentration and does not enhance insulin secretion in the presence of a fasting physiological glucose concentration.

5. The method of any one of claims 1-4 wherein the diabetes mellitus is type 2 diabetes mellitus.

6. The method of any one of claims 1-4 wherein the diabetes mellitus is maturity onset diabetes of the young.

7. The method of any one of claims 1-4 wherein the pharmaceutical composition is administered orally.

8. The method of any one of claims 1-4 wherein the agent does not substantially alter insulin secretion in the presence of a fasting physiological glucose concentration.

9. The method of any one of claims 1-4 wherein the candidate agent is membrane permeable.

10. The method of claim 9 wherein the membrane is at least one of the membranes selected from the group consisting of a plasma membrane and a mitochondrial membrane.

11. The method of claim 10 wherein the mitochondrial membrane is selected from the group consisting of an inner mitochondrial membrane and an outer mitochondrial membrane.

12. A method for determining the presence of a mitochondrial calcium/ sodium antiporter polypeptide in a biological sample comprising:

contacting a biological sample containing a mitochondrial calcium/ sodium antiporter polypeptide with a mitochondrial calcium/ sodium antiporter ligand under conditions

and for a time sufficient to allow binding of the mitochondrial calcium/ sodium antiporter ligand to a mitochondrial calcium/ sodium antiporter polypeptide; and

detecting the binding of the mitochondrial calcium/ sodium antiporter ligand to a mitochondrial calcium/ sodium antiporter polypeptide, and therefrom determining the presence of a mitochondrial calcium/ sodium antiporter polypeptide in said biological sample.

13. The method of claim 12 wherein the mitochondrial calcium/ sodium antiporter ligand comprises Compound No. 1 or a derivative thereof.

14. The method of claim 12 wherein the mitochondrial calcium/ sodium antiporter ligand is detectably labeled.

15. The method of claim 14 wherein the detectably labeled mitochondrial calcium/ sodium antiporter ligand comprises a radiolabeled substituent.

16. The method of claim 15 wherein the radiolabeled substituent is selected from the group consisting of ^{125}I, ^{131}I, ^{3}H, ^{14}C, ^{45}Ca and ^{35}S.

17. The method of claim 12 wherein the detectably labeled mitochondrial calcium/ sodium antiporter ligand comprises a fluorescent substituent.

18. The method of claim 14 wherein the detectable detectably labeled mitochondrial calcium/ sodium antiporter ligand comprises covalently bound biotin.

19. A method for isolating a mitochondrial calcium/ sodium antiporter from a biological sample, comprising:

contacting a biological sample suspected of containing a mitochondrial calcium/ sodium antiporter polypeptide with a mitochondrial calcium/ sodium antiporter ligand under

conditions and for a time sufficient to allow binding of the mitochondrial calcium/ sodium antiporter ligand to a mitochondrial calcium/ sodium antiporter polypeptide; and

recovering the mitochondrial calcium/ sodium antiporter polypeptide, and thereby isolating a mitochondrial calcium/ sodium antiporter from a biological sample.

20. The method of claim 19 wherein the mitochondrial calcium/ sodium antiporter ligand is covalently bound to a solid phase.

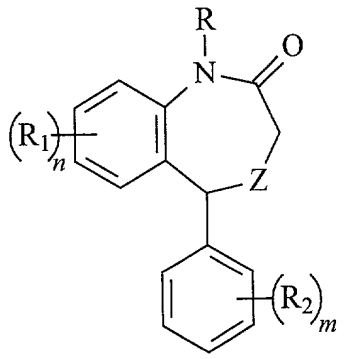
21. The method of claim 19 wherein the mitochondrial calcium/ sodium antiporter ligand is non-covalently bound to a solid phase.

22. The method of any one of claims 1-4 further comprising administering to the subject one or more agent that lowers circulating glucose concentration in the subject.

23. The method of claim 22 wherein the agent that lowers circulating glucose concentration is selected from the group consisting of insulin, an insulin secretagogue, an insulin sensitizer, an inhibitor of hepatic glucose output and an agent that impairs glucose absorption.

24. The method of claim 23 wherein the insulin secretagogue is selected from the group consisting of a sulfonylurea compound and a nonsulfonylurea compound.

25. The method of any one of claims 1-4 wherein the agent has the following structure:



or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof,

wherein

Z is O, S, S(=O) or $S(=O)_2$;

R is hydrogen, alkyl or substituted alkyl;

R_1 and R_2 are the same or different and at each occurrence are independently halogen, cyano, nitro, mono- or di-alkylamino, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl; and

n and *m* are the same or different, and independently 0, 1, 2, 3 or 4.

26. The method of claim 25 wherein Z is oxygen.

27. The method of claim 25 wherein Z is sulfur.

28. The method of claim 25 wherein *n* is 1.

29. The method of claim 25 wherein *m* is 1.

30. The method of claim 28 wherein R_1 is halogen.

31. The method of claim 29 wherein R_2 is halogen.

32. The method of claim 30 wherein R_1 is halogen at the 8-position.

33. The method of claim 31 wherein R_2 is halogen at the 2-position.

34. The method of claim 25 wherein R is hydrogen

35. The method of claim 25 wherein R is substituted alkyl.

36. The method of claim 35 wherein alkyl is substituted with $-C(=O)OR_a$.

37. The method of claim 36 wherein R_a is hydrogen or alkyl.

38. The method of claim 35 wherein alkyl is substituted with $-CONR_a\{alkanediyl\}OR_b$ or $-CONR_c\{alkanediyl\text{-}O)_{1\text{-}6}(alkanediyl)NR_aR_b$,.

39. The method of claim 38 wherein $-CONR_a\{alkanediyl\}OR_b$ is $-CONH(CH_2)_2OCH_3$.

40. The method of claim 38 wherein $-CONR_c\{alkanediyl\text{-}O)_{1\text{-}6}(alkanediyl)NR_aR_b$ is $-CONH\{(CH_2)_2O\}_2(CH_2)_2NH_2$.